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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/444,790	05/19/1995	MANFRED BROCKHAUS	9189	5612

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	08/444,790	BROCKHAUS ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,102,103,105-107,110,111,113,114,119-121,123-137 and 139-144* is/are pending in the application.

4a) Of the above claim(s) *139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,102,103,105-107,110,111,113,114,119-121,123-137 and 140-144* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 May 1995* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/6/2006; 1/22/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 62,102,103,105-107,110,111,113,114,119-121,123-137 and 139-144.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 10/6/06 has been entered in full. Claims 62, 102, 105, 106, 107, 114, 121-123, 132 and 134 are amended. Claims 66, 67, 104, 112, 122 and 138 are canceled (claims 1-61, 63-65, 68-101, 108, 109 and 115-118 were canceled previously). New claims 139-144 are added.

The supplemental amendment of 11/14/06 has been entered in full. Claim 140 is amended.

Election/Restrictions

Newly submitted claim 139 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 139 is directed to an *in vivo* method of binding human TNF comprising administering to a subject the pharmaceutical composition of claim 137. The products of claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121, 123-137 and 140-144 (proteins and compositions thereof) are related to the method of claim 139 as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the proteins of claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121, 123-137 and 140-144 can be used in an *in vivo* method of binding human TNF comprising administering a protein, but the proteins can also be used in methods of screening for compounds that modulate ligand (TNF) binding activity, or to isolate the ligand (TNF) to the protein from a biological sample, which are a materially different methods.

Since Applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 139 is withdrawn from

consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121, 123-137 and 140-144 are under consideration in the instant application.

Priority

Applicants have amended the priority statement on the first page of the specification such that the instant application claims priority under 35 U.S.C. § 119 to European Patent Application Number 90116707.2 (now Patent Number EP 0417563), filed August 31, 1990. Acknowledgment is made of applicant's claim for foreign priority. Such a claim is permitted under 37 C.F.R. § 1.55. It is noted, however, that applicant has not filed a certified copy of the 90116707.2 application as required by 35 U.S.C. 119(b). Furthermore, Applicants have not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of foreign application 90116707.2. It is noted that an application data sheet was filed on 2/21/06, but this application data sheet does include an acknowledgement of the 90116707.2 application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date.

For these reasons, the instant application does not merit priority to the 8/31/90 filing date of 90116707.2.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (4/3/06).

The objection to the specification at pg 4 is *withdrawn* in view of Applicants amendments to the specification. However, please note the new objection to the specification set forth below.

All rejections of claims 66, 67, 104, 112, 122 and 138 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 123, 124, 132 and 133 under 35 U.S.C. § 112, first paragraph at pg 5-6 for lack of enablement is *withdrawn* in view of the Declaration of Biological Culture Deposit under Terms of the Budapest Treaty submitted 10/6/06 and the amendments to the specification to indicate the identifying information required set forth in 37 C.F.R. § 1.809(d).

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 62, 102, 103, 105, 106, 107, 110, 111, 113, 114, 119-121 and 123-137 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 6-9 of the 4/3/06 Office Action.

It is noted that Applicants' 10/6/06 amendments to the claims have changed the scope of the genus of proteins encompassed by the claims. The genus of proteins encompassed by claims 62, 105, 107, 119, 120, 121, 123, 124 and 129-132, now requires that the soluble fragment must be able to bind to human TNF, and that the insoluble receptor from which the soluble fragment is derived must comprise the seventeen amino acids of SEQ ID NO: 10 rather than a fragment of SEQ ID NO: 4 (it is noted that SEQ ID NO: 4 does not comprise the seventeen amino acids of SEQ ID NO: 10). Claims 102, 106, 113, 125-128, 110, 133, 134 and 136 also require that the soluble fragment comprise the four amino acids of SEQ ID NO: 12 and the four amino acids of SEQ ID NO: 8. Claims 103, 111, 133 and 135 also require that the soluble fragment comprises the seventeen amino acids of SEQ ID NO: 10 in addition to SEQ ID NOs: 12 and 8. Claims 114 and 135 relate to compositions comprising said proteins.

The basis of the written description rejection set forth previously is restated in view of the amended claims.

The amended claims are genus claims because the claims are directed to variant proteins that specifically bind human TNF. The proteins are fusion proteins that comprise two parts: (a) a TNF-binding soluble fragment of a receptor; and (b) "all of the domains of the constant region of a human immunoglobulin heavy chain other than the first domain of said constant region". In claim 62, part (a) encompasses a protein comprising any TNF-binding soluble fragment of an insoluble human TNF receptor

comprising SEQ ID NO: 10. The sequence of SEQ ID NO: 10 consists of 17 of the first 18 amino acids of the full-length human tumor necrosis factor type II receptor (TNF-IIR or TNF2R; also known variously as p75 or p80 based on the molecular weight on a SDS-polyacrylamide gel). The full-length mature human TNF2R is 439 amino acids, with the extracellular portion consisting of amino acids 1-235 (see pg 233 and Figure 1 of Dembic et al, 1990. Cytokine. 2(4); 231-7; cited previously). In addition to SEQ ID NO: 10, the instant specification discloses another partial sequence of said receptor designated as SEQ ID NO: 4 that is missing amino acids 1-48 found in the full-length mature TNF2R. Therefore, instant SEQ ID NO: 4 is missing the first 48 amino acids of the extracellular domain (approximately 20% of the extracellular domain). Together, SEQ ID NO: 4 and 10 consist of only a portion of the TNF2R extracellular domain (residues 1-7, 9-18 and 49-235).

The relevant art teaches that the extracellular domain of human TNF2R is the portion of the protein that binds human TNF. Chan et al teaches, "The deletion of PLAD [protein-ligand assembly domain] from either p60 or p80 completely abrogated ligand binding (Table 1 and Fig. 1E)" (pg 2351 of Chan et al. 2000, Science, 288: 2351-2354; cited previously). Chan teaches that the PLAD is amino acids 10-54 of the receptor (pg 2351). Furthermore, specific single or double mutations in this region in the TNFRI receptor "eliminated TNF-α binding" (pg 2351). Chan concludes "the PLAD is physically distinct from the ligand contact domain but nonetheless essential for efficient TNF-α binding and receptor function." In view of the teachings of Chan, the truncated receptor of SEQ ID NO: 4 taught by Applicants would not have the ability to bind TNF, as required by the claims. The additional sequence of SEQ ID NO: 10 is not sufficient to make up for the missing region as the combination of SEQ ID NO: 4 and SEQ ID NO: 10 would still produce a receptor missing critical residues 19-48.

The broadest claims encompass <u>any</u> TNF-binding soluble fragment of a 75 kD insoluble TNF-binding receptor that comprises SEQ ID NO: 10. Therefore, this fragment can be as long as the entire extracellular domain (comprising the entirety of SEQ ID NO: 4), or it can be as small as one amino acid from SEQ ID NO: 4. However,

Applicants do not teach any amino acid sequence(s) that can actually bind TNF. Applicants do not disclose any teachings demonstrating that SEQ ID NO: 4 (missing 48 amino acids of the extracellular domain of TNFR2) can bind to TNF. Therefore, the specification has not described a single example of the sequence of a protein in the claimed genus that can actually bind human TNF.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of any member of the genus of claimed polypeptides. Neither the specification nor the claims describe a TNF2R protein sequence that can bind to TNF-α. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides,

and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the instant claims do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see pg 1115).

Applicants' arguments (10/6/06; pg 26-30) as they pertain to the above rejection have been fully considered but are not found to be persuasive for the following reasons. Each of Applicants' arguments is addressed in turn.

In the response dated 10/6/06, Applicants argue that there is sufficient evidence to show that Applicants were in possession of a representative number of species to support the claimed genus. Applicants argue that there was disclosure of a variety of TNFR fragments with TNF-binding activity, and the functional characteristic of TNF-binding coupled with a known correlation between this function and the sequence structure. Applicants point to MPEP § 2163. Applicants argue that the specification discloses the full-length amino acid sequence of TNFR and TNF-binding deletion fragments thereof by citing Smith et al (1990).

Applicants' arguments have been fully considered but are not found persuasive. The specification does not provide evidence that Applicants were in possession of any TNF-binding soluble fragments of an insoluble 75 kD TNF-binding receptor comprising SEQ ID NO: 10. While the sequence of the entire extracellular domain of the 75 kD TNF

receptor was publicly available in the references of Smith (1990) and Dembic (1990) at the time of filing of the instant application, there is no description in the instant specification of these specific full-length sequences, or any description that suggests using these full-length sequences in the claimed fusion proteins. While the specification cites Smith (1990) on page 10, the specification does not contemplate use of the sequence of the full-length extracellular domain of the receptor taught in Smith. The only paragraph in the specification that refers to Smith (1990) states:

> "That is to say, the present invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in Figure 1 or Figure 4, whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP. One sequence which results from such a deletion is described, for example in Science 248, 1019-1023, (1990)" (pg 10, lines 1-10)

The last sentence of this paragraph is the only sentence that refers to Smith, and this sentence only refers to "one sequence" in Smith that results from a "such a deletion". The phrase "such a deletion" must refer to the "deletions" recited in the previous sentence, which are deletions made to the nucleotide sequence of Figure 1 or Figure 4. Therefore, this paragraph refers solely to nucleotide sequences with deletions of one or more nucleotides to the sequences given in Figure 1 or Figure 4, and the proteins encoded by said nucleotides. Figure 4 shows a partial cDNA sequence of the 75 kD TNF receptor having less than the full-extracellular domain; therefore any deletions made to this sequence would not achieve a nucleotide sequence encoding the full-length extracellular domain presented in Smith. Therefore, the reference to Smith in the specification does not refer to a nucleotide sequence encoding the full-length extracellular domain of the receptor disclosed in Smith.

Furthermore, the reference to Smith cannot refer to the region consisting of the "NH2-terminal 162 amino acids (positions 39 to 200)" (it is noted that instant SEQ ID NO: 4 begins at residue 71 according to Smith). While Smith refers to the "NH2-terminal 162 amino acids (positions 39 to 200)" and teaches that "[p]resumably, it is this NH2-terminal region that contains the TNF binding site" this is a description of a domain

found within a longer protein, not a description of deletion(s) made to a nucleotide sequence that results in a sequence encoding this fragment of the sequence. There is no description in Smith that such a region, when isolated, retains TNF-binding. Therefore, while the instant claims encompass a fusion protein comprising the full-length extracellular domain sequence disclosed by Smith and a portion of an immunoglobulin molecule, there is no indication at the time of the filing that the instant specification described a fusion protein made with this particular species found within the vast genus of fusion protein variants encompassed by the claims. Applicants' disclosure at the time of filing would not have lead the skilled artisan to the particular species of fusion protein comprising the entire extracellular domain found in Smith. In absence of a description of the full-length extracellular domain of the 75 kD receptor for use in Applicants' claimed invention, Applicants did not have possession of the claimed invention at the time of filing.

Applicants further argue at pg 27 that the reference of Dembic (1990; cited previously) was published prior to the filing date of the instant application and indicates that Applicants had possession of the complete amino acid sequence of p75 TNFR.

This argument has been fully considered but is not found to be persuasive. The instant specification as filed contains no reference to the teachings of Dembic, and therefore there is no teaching in the instant specification indicating that the sequences disclosed in Dembic are relevant to the proteins of the instant invention, including the claimed fusion proteins. Therefore, while the instant claims encompass a fusion protein comprising the full-length extracellular domain sequence taught by Dembic and a portion of an immunoglobulin molecule, there is no indication at the time of the filing that the instant specification contemplated a fusion protein made with this particular species found within the vast genus of fusion protein variants encompassed by the claims. Applicants' disclosure at the time of filing would not have lead the skilled artisan to the particular species of fusion protein comprising the entire extracellular domain found in Dembic.

Applicants further argue that accessible literature sources are relevant to fulfilling the written description requirement even though sequences are not recited in the specification. In support, Applicants point to *Falkner et al v. Inglis et al* (2006).

This argument has been fully considered but is not found to be persuasive. The fact patterns of the case cited by the Applicants and of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. The disclosure of the Inglis '040 application does not have a description of the poxvirus essential genes and relies on a prior art disclosure of poxvirus essential genes. However, the Inglis '040 application does have a detailed description and working examples of closely related herpes virus-based vaccines. The specification of the Inglis '040 application makes several assertions that the teachings regarding herpes virus-based vaccines can be applied to a poxvirus-based vaccine. So, the disclosure of the Inglis '040 application describes, in great detail, how to make a vaccine with one type of virus (herpes), which provides a description for the skilled artisan regarding how to make a vaccine with a second type of virus (poxvirus). This is distinguished from the instant case because there is nothing disclosed in the instant specification that is analogous to the herpes virus-based vaccine of Inglis, upon which the skilled artisan could rely as guidance to extend the teachings of the specification from a different receptor to the full-length TNF receptor.

Applicants further argue (pg 28) that the specification describes a variety of soluble and insoluble fragments of TNFR that are capable of binding TNF including a protein characterized by apparent molecular weights of 75 kD or 65 kD and DNA sequences characterized by deletions of one or more nucleotides of Figure 1 or Figure 4. Applicants argue that these partial sequences can be used to determine "those partial sequences which code for soluble TNF-BP fragments" (pg 28).

Applicants' arguments have been fully considered but are not found to be persuasive. As described above, the specification does not support possession of a fusion protein comprising the full-length extracellular domain of a 75 kD TNF-binding insoluble receptor. Furthermore, even if the specification provided a written description

of a fusion proteins comprising the full-length extracellular domain of the TNFR-2 receptor as taught by Smith (1990) or Dembic (1990), the specification as filed does not provide a written description of the vast genus of protein variants encompassed by the claims. The scope of the amended claims is such that the potential TNF-binding fragment of the receptor can comprise the entire extracellular domain or any fragment thereof as small as one amino acid that retains TNF-binding. However, there is no description in the instant specification of essential TNF binding regions found within this sequence, such that one of skill in the art would reasonably believe that Applicants were in possession of the large genus of TNF-binding fragments encompassed by the claims. The specification does not provide any structural correlation between the partial sequences of the 75 kD TNF-binding insoluble receptor (e.g., SEQ ID NOs: 4 or 10) and the ability to bind TNF. Furthermore, the claims also encompass fragments of protein variants in which one or more amino acids in the TNFR-2 extracellular domain has been altered by mutation. The specification specifically contemplates protein variants in which one or more amino acids are deleted, added, or substituted (see page 10, lines 1-10, and page 11, lines 12-30). Applicants have not provided a representative number of species of the TNF-binding fragments and variants encompassed by claims.

Applicants further argue that the Smith 1990 article and the Dembic 1990 article disclose at least three different fragments including the full 235-residue extracellular domain, an N-terminal 162-residue cysteine-rich fragment that contains the TNF-binding site, and a naturally occurring truncated fragment that is missing at least he first four N-terminal amino acids of the mature TNFR sequence (pg 28).

Applicants' arguments have been fully considered but are not found to be persuasive. As described above, the specification does not support possession of a fusion protein comprising the full-length extracellular domain of a 75 kD TNF-binding insoluble receptor. Nor does the specification indicate possession of fusion protein comprising an N-terminal 162-residue cysteine-rich fragment that contains the TNF-binding site or a fusion protein comprising a naturally occurring truncated fragment that is missing at least he first four N-terminal amino acids of the mature TNFR sequence.

As stated above, the N-terminal 162-residue cysteine-rich domain taught by Smith, 1990 is a domain found within the full-length protein and is not an isolated fragment that can bind to TNF. There is no description in the instant specification or Smith as to whether this domain, when isolated from the context of the full-length protein, can bind to TNF. Furthermore, Smith only hypothesizes that this region can bind TNF, does not provide any direct evidence that this region binds TNF, and does not demonstrate that any region of the extracellular domain of the receptor can tolerate mutations and retain TNF binding.

Applicants further argue that the reference to a "human" p75 TNFR sequence refers to naturally occurring human p75 TNFR amino acid sequence.

This argument has been fully considered but is not found to be persuasive. The specification does not provide a limiting definition of "insoluble human TNF receptor" as recited in the claim. Therefore, the term "insoluble human TNF receptor" does not limit the receptor to any particular naturally occurring human receptor, but includes allelic variants as well as artificial receptors with one or more amino acid mutations to the sequence of the insoluble human TNF receptor. As set forth above, the claims encompass a vast genus of fragments of human TNF receptors.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 102, 103, 105, 106, 107, 110, 111, 113, 114, 119-121, 125-131 and 134-137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dembic et al (Cytokine, Vol. 2, No. 4 (July) 1990: 231-237; cited previously) in view of Capon et al, U.S. Patent No. 5,116,964 (published 5/26/92 and filed 11/22/89; cited previously). This rejection was set forth at pg 9-12 of the 4/3/06 Office Action.

Applicants have amended the scope of the proteins encompassed by the claims. The basis of the rejection is herein restated in view of the claim amendments.

Claims 62, 102, 103, 105, 106, 107, 110, 111, 113, 114, 119-121, 125-131 and 134-137 each encompass a genus of variant polypeptides. While the scope of each genus varies, each encompasses the following polypeptide: a purified protein, recombinantly produced in CHO cells, that specifically binds human TNF and comprises parts (a) and (b). Part (a) of each claim encompasses a TNF-binding soluble fragment of an insoluble human TNF receptor; wherein said receptor has three characteristics: (i) binds TNF; (ii) 75 kD molecular weight; and (iii) comprises SEQ ID NO: 10, 12, 8, 9 and 13. Part (b) of each claim encompasses "all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region". The narrowest claims limit immunoglobulin heavy chain to human IgG1; however, all of the claims encompass this limitation.

Dembic teaches the full-length amino acid sequence of the 75 kD Tumor Necrosis Factor receptor (see pg 232 and Figure 1). This membrane-bound (insoluble) receptor meets the three characteristics of the receptor of claim 62: (i) it binds TNF; (ii) 75 kD; and (iii) comprises the following sequences (as shown in Figure 1): SEQ ID NO: 8 (VFCT; residues 43-47); SEQ ID NO: 9 (NQPQAPGVEASGAGEA; residues 323-340); SEQ ID NO: 10 (LPAQVAFTPYAPEPGSTC; residues 1-18; this sequence falls within the genus of LPAQVAFXPYAPEPGSTC); SEQ ID NO: 12 (LCAP; residues 114-117) and SEQ ID NO: 13 (VPHLPAD; residues 278-284). Dembic further teaches the extracellular domain of this receptor forms a soluble fragment that binds TNF (see pg 235, column 1). Dembic does not teach a fusion of the extracellular domain of the 75 kD TNF receptor with a portion of the constant region of a human immunoglobulin heavy chain.

Capon teaches (Example 4, starting at column 40) a fusion of truncated murine lymphocyte homing receptor (MHLR) to the Fc region of human IgG1 ("These truncated proteins are all joined to a human heavy chain γ 1 region just upstream of the hinge domain (H) such that these chimeras contains the two cysteine residues of the hinge

responsible for dimerization as well as the CH2 and CH3 constant regions." The Fc region consists of the CH2 and CH3 domains of the constant region but does not include the CH1 domain. Capon further teaches that the hybrid immunoglobulins can be used for affinity purification of ligands (col 22, lines 5-6). Capon further teaches recombinant production of hybrid immunoglobulins in cell culture (col 26, lines 24-26). Capon further teaches that CHO cells are suitable eukaryotic cells for production of hybrid immunoglobulins (col 29, line 37). Capon further teaches purification of the hybrid immunoglobulin from cell cultures following expression in host cells (col 30, line 26-27). Capon further teaches placement of the purified hybrid immunoglobulin in "sterile, isotonic formulations" that are "preferably liquid" and "ordinarily a physiologic salt solution" (col 31, lines 4-8). Such solutions meet the definition of a "pharmaceutically acceptable carrier material" (as in claim 114).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to fuse the extracellular portion of the TNF receptor sequence taught by Dembic to the Fc region taught by Capon, and to recombinantly produce the protein in CHO cells and purify the protein produced as taught by Capon. The person of ordinary skill in the art would be motivated to do so in order to produce and purify the TNF receptor-Ig fusion for use in affinity purification of the TNF ligand. The person of ordinary skill in the art would have expected success because Capon teaches that Ig fusions can be made with a wide variety of proteins, and teaches all of the techniques for recombinant production of hybrid immunoglobulins in CHO cells and purification of the produced protein.

With respect to claims 114 and 137, the recitation of "a pharmaceutical composition" in the preamble of the claim is interpreted as an intended use and bears no accorded patentable weight. Therefore, the claims encompass any composition comprising a recombinant protein of claims 62, 107, 134 or 135 (claim 114) or claim 105 (claim 137) and a pharmaceutically acceptable carrier material. As described above, Capon teaches compositions comprising a hybrid immunoglobulin in a pharmaceutically acceptable carrier material. It would have been obvious to the person of ordinary skill in

the art at the time the invention was made to further include the hybrid TNF receptor-immunoglobulin in a pharmaceutically acceptable carrier material. The person of ordinary skill in the art would be motivated to do so in order to resuspend the hybrid immunoglobulin for use following purification. The person of ordinary skill in the art would have expected success because Capon teaches the necessary procedures for purification and resuspension of the hybrid immunoglobulin.

Applicants' arguments (10/6/06; pg 12-26) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Each of Applicants' arguments is responded to in turn.

Applicants argue that fusion of TNFR soluble fragments to immunoglobulin fragments for affinity purification does not provide motivation for construction of homodimeric fusion proteins (such as would be formed by the claimed proteins); because one of skill in the art would have had more certainty of success in constructing a monomeric antibody fusion that bound TNF. Applicants argue that TNF was known to form a biologically active trimer prior to Applicants' filing date. Applicants point to Wingfield et al (1987) and Smith et al (1987). Applicants submit that the location of the receptor binding sites on the TNF trimer, three-dimensional structure of the TNF receptor, and the interaction of the receptor with the TNF trimer were unknown. Applicants submit that there was uncertainty in whether the spatial configuration of the dimeric fusion protein would allow it to bind a trimeric ligand in view of the lack of knowledge of steric distances between the two TNF-binding sites in the dimer, the degree of flexibility required to accommodate the TNF trimer and whether the three-dimensional structure of the TNF receptor would be retained when fused to a relatively large heavy chain fragment. In support Applicants point (on page 17 of the response) to Exhibit B of the Declaration under 37 C.F.R. § 1.132 of Dr. Werner Lesslauer submitted 1/12/05 as stating that spatial geometry of the receptor-binding site was unknown and that it would have been entirely possible for an IgG fusion with the receptor to create a spatial configuration which could bind TNF α.

These arguments have been fully considered but are not found to be persuasive. The references of Wingfield (1987), Smith (1987) and the Declaration under 37 C.F.R. § 1.132 of Dr. Werner Lesslauer (attached as Exhibit B to Applicants' 1/12/05 response) have been fully considered but are not sufficient to establish a lack of motivation to combine the teachings of the references of Dembic and Capon. The conclusion in the Declaration regarding the ability of an Ig-receptor fusion to bind TNF is based on the ability of the ligand to form trimers and that, at the time of filing, the structure of the TNF binding site on the receptor was unknown. The Examiner does not dispute that the TNF ligand can form biologically active trimers, or that the structure of the binding site on the receptor was not known at the time of filing. However, the prior art also appreciates that at the time of filing that the TNF ligand trimer was known to bind to two receptor molecules (see Smith et al, 1989. Journal of Biological Chemistry. 14646-15652). Therefore, the state of the prior art provides a motivation to use a dimeric form of the receptor for binding TNF ligand as taught by Capon and the skilled artisan would have a reasonable expectation of success that when the extracellular domain of the receptor taught by Dembic was combined with the Fc region taught by Capon (which is functionally dimeric) that a dimeric fusion protein would be produced that would be able to bind the trimeric TNF ligand. In view of the teachings of the prior art, the fact that the TNF alpha ligand was trimeric and that the structure of the binding site on the receptor was not known does not detract from the reasonable expectation that a dimeric form of the receptor could be used to successfully bind the ligand.

Applicants further argue that Capon teaches away from construction of the claimed fusion proteins (pg 14-16). Applicants argue that the main focus of Capon is *in vivo* administration; that the heavy chain constant region was known at the time to filing to be a pro-inflammatory agent; and that one of skill in the art would not have motivated to fuse such a pro-inflammatory agent to an anti-inflammatory agent such as soluble TNFR.

Applicants' arguments have been fully considered but are not found persuasive. As stated in MPEP 2123, "Patents are relevant as prior art for all that they contain" and "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain" and "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments." The Examiner does not dispute that Capon provides teachings regarding *in vivo* administration, or that the heavy chain constant region contains regions that elicit the pro-inflammatory effector functions of immunoglobulins, or that soluble TNFR would be a an anti-inflammatory agent. However, as set forth previously and reiterated above, Capon also teaches that the hybrid immunoglobulins can be used for affinity purification of ligands (col 22, lines 5-6). This is an *in vitro* use for which an *in vivo* anti-inflammatory activity of the heavy chain constant region is not relevant.

Applicants further argue that the 103 rejection should be withdrawn in view of a number of unexpected results associated with the claimed TNF-binding fusion proteins. Applicants present data supporting three categories of unexpected results: lack of aggregation ability; markedly reduced immunoglobulin effector function; and "binding affinity, kinetic stability and potency".

Applicants' arguments have been fully considered but are not found persuasive. The evidence of unexpected results presented by Applicants is not sufficient to overcome the rejection. Applicants' putative unexpected results appear to be generated using a fusion protein comprising the full-length extracellular domain of the insoluble 75 kD TNF binding receptor and portions of an immunoglobulin molecule. However, as set forth above, in the section "Claim Rejections - 35 U.S.C. 112, 1st paragraph, written description", the specification does not provide a description of this particular species of fusion protein. There is no conception in the specification at the time of filing of this particular species of fusion protein. Therefore, the evidence of unexpected results found

with this particular species of receptor-Ig fusion is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon.

New Rejections necessitated by Applicants' amendment

Specification

The amendment filed 11/14/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is the statement: "deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942." This phrase was inserted into page 10, line 11 of the specification in the following manner: "DNA sequences which code for insoluble (deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred". However, this amendment does not clearly indicate the exact nature of the sequence that has been deposited. The deposit appears to be of an unspecified DNA sequence somehow related to an insoluble fraction of TNF-binding protein having an apparent molecular weight of 65 or 75 kD. It is not clear if, for example, the DNA sequence is the "the partial cDNA sequence shown in Figure 4" referred to earlier on page 10, or if the sequence is a new sequence that is not described in the specification as filed, for example a cDNA sequence comprising the full-length extracellular domain of the 75 kD receptor. On 11/14/06, Applicants also submitted the "Third Declaration of Dr. Werner Lesslauer under 35 U.S.C. § 1.312", which indicates that the deposited material is "[a] DNA construct designated N227 containing DNA sequence which includes sequence encoding the signal sequence and the extracellular domain of human p75 tumor necrosis factor receptor (TNFR) was constructed on a date before September 10, 1990" (pg 1). However, the declaration by Dr. Lesslauer is not sufficient to establish that the material referred to in the 11/14/06 amendment to the specification is not new matter, because the DNA construct

designated N227 referred to by Dr. Lesslauer is not clearly disclosed in the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 140-144 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel biological materials. Specifically, new claims 140-144 encompass proteins comprising a "human tumor necrosis factor (TNF) binding soluble fragment of the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC on October 17, 2006 under the accession number PTA 7942". Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C § 112 may be satisfied by a deposit of the biological materials. It is noted that the specification indicates (pg 10) that DNA sequences which code for insoluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD have been deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA7942.

However, the indicated deposit is not sufficient to meet the requirements for deposit for the following reasons.

If a deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicant(s) or person associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over

his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R.§1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, should be submitted stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C.F.R.§1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

It is noted that a declaration related to this deposit was submitted 11/14/06 and is titled "Third Declaration of Dr. Werner Lesslauer under 35 U.S.C. § 1.132". However, this declaration does not contain the required information set forth above.

Even if the required information described above is provided by affidavit or declaration, the deposit will not meet the deposit requirement for the following reasons. Specifically, the deposit requirements require that the identifying information set forth in 37 C.F.R. § 1.809(d) should be added to the specification. See MPEP § 1.809. The

instant specification does not contain the identifying information set forth in 37 C.F.R. § 1.809(d) for the following reasons. 37 C.F.R. § 1.809(d) states, "For each deposit made pursuant to these regulations, the specification shall contain: ... (3) A description of the deposited material sufficient to specifically identify it and to permit examination..."

In the instant case, the specification was amended to recite "DNA sequences which code for insoluble (deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred". This statement is not sufficient to specifically identify the nature of the deposited sequence. For example, the deposited sequence could be any one or more DNA sequences which code for insoluble fractions of TNF-binding protein having an apparent molecular weight of 65 kD/75 kD. The description of the deposit is not sufficient to indicate the deposited material is a DNA sequence that was described in the specification at the time of filing. On 11/14/06, Applicants also submitted the "Third Declaration of Dr. Werner Lesslauer under 35 U.S.C. § 1.312", which indicates that the deposited material is "[a] DNA construct designated N227 containing DNA sequence which includes sequence encoding the signal sequence and the extracellular domain of human p75 tumor necrosis factor receptor (TNFR) was constructed on a date before September 10, 1990" (pg 1). However, the DNA construct designated N227 referred to by Dr. Lesslauer is not clearly disclosed in the specification as originally filed, and therefore the specification as originally filed does not teach how to make the claimed product.

In view of the lack of a specific description of the deposited material, the specification does not enable the skilled artisan to make and/or use the claimed invention of claims 140-144.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claim 140-144 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

New claims 140-144 were submitted with the 10/6/06 response. Claim 140 was subsequently amended 11/14/06 and is directed to a protein comprising the "human tumor necrosis factor (TNF) binding soluble fragment of the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC on October 17, 2006 under accession number PTA 7942". The "Third Declaration of Dr. Werner Lesslauer under 35 U.S.C. § 1.132" submitted 11/14/06 states that the "DNA construct designated N227 containing DNA sequence which includes sequence encoding the signal sequence and the extracellular domain of human p75 tumor necrosis factor receptor (TNFR) was constructed on a date before September 10, 1990" and that "[t]he DNA sequence within construct N227 is a DNA sequence identified in the above referenced application at page 10, line 34". Applicants' amendments to the specification at page 10 made 11/14/06 introduce deposit information to the following sentence: "DNA sequences which code for insoluble (deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred".

The claims indicate that the plasmid deposited with the ATCC contains a cDNA insert. The only cDNA insert in the specification related to the 65 kD/75 kD TNF-binding protein is the partial cDNA sequence that is presented in the application in Figure 4 and SEQ ID NO: 4. This sequence does not contain any signal sequence. Dr. Lesslauer's statements in the 11/14/06 Declaration indicate that this DNA sequence includes a "signal sequence". While the description in the specification does not clearly indicate what DNA sequence was deposited, it appears that Applicants may have deposited a plasmid containing a DNA sequence including a signal sequence, such as DNA

encoding the full-length TNFR-2 receptor (65 kD/75 kD TNF-binding protein). However, there is no support in the specification at the time of filing for the specific cDNA encoding the full-length TNFR-2 receptor. Furthermore, there is no clear description in the specification as originally filed of the DNA construct designated N227. There is no conception of the specific construct, nor does the concept of the specific genus flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for the proteins encompassed by the claim 140. Claims 141-144 are included in this rejection because they depend from claim 140.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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